Physiology of Parturition

Introduction

Parturition is a special topic. It stands apart as the least understood by medical science and the most difficult (and the last of 314 Basic Science lessons!) for Dr. Williams to complete. Judging from the seemingly foreign language used in histology and physiology textbooks, Dr. Williams thought that there was something about parturition that put it beyond his knowledge of human physiology. As it turns out, there isn't.

In this lesson, we translate things. We make things fit. We don't claim to have everything figured out—it seems that no one does. But what we do here is take the current knowledge of gestation, delivery, and recovery and apply it to humans. You read that right: the current knowledge, what you read in textbooks, comes from the study of rats. Humans are not rats. Humans are more complicated than rats. But just barely. We will also translate that information, written in the specialized vocabulary of the textbooks, into language you already know. Do you know what prostaglandin H synthetase 1 is? Neither did we. And we never needed to. But GPCRs? Smooth muscle? How calcium causes contractions? We all know these things extremely well. We tell the story of a confusing topic, using the modular components of health and disease that we have been teaching you throughout the Basic Sciences: GPCRs, prostaglandins, calcium to contract, cAMP to relax; steroid hormones, gene transcription regulation, contraction-associated proteins, quiescence-associated proteins, endocrine and paracrine signaling . . . topped with a heaping spoonful of unknowns-to-medical-science.

Phases of Parturition

Huge respect to those who came before and defined the events of gestation, labor, delivery, and recovery. They got it right. Only, they didn't realize it. They correctly defined the four phases of parturition, but they missed the timing and mechanisms of those phases in humans. Because humans are more complex than rats, and most of medical science's understanding stems from studying rats, the timing and mechanisms that are well understood (in rats) do not map exactly onto humans.

In a nutshell, the traditional teaching is that there are four phases of parturition, which is traditionally defined as the birthing of one's young. Also traditionally, most people understand the birthing of one's young to consist of "labor and delivery"—but that is only phase 3 of the phases of parturition. So, we start with a sense that *parturition* does not mean what we think it means . . . it includes ovulation, fertilization, implantation, and most of gestation (taken together as phase 1); preparation for labor and delivery (phase 2); labor and delivery (phase 3); and after labor and delivery (phase 4).

Miraculously, these four phases are the same in rats and humans. However, their relative timing and mechanisms are more complicated in humans. Rats gestate for 21 days, humans gestate for 40 weeks. Rat phase 1 lasts for about 90% of the pregnancy; human phase 1 is 60% (until week 24). Rats spend 10% of their pregnancy in phase 2, compared to 40% for humans. But both humans and rats deliver their young through the vagina via dilation of the cervix and contraction of the myometrium—phase 3. And both humans and rats restore their uterus, cervix, and vagina to the prepregnant state rapidly after delivery—phase 4. So, except for the timing of events, things seem to line up.

However, when we turn to the mechanisms, the phrase *phases of parturition* finally reveals itself as a misnomer. Just as the ovarian cycle is an ever-changing, progressive process, so too are the human *phases of parturition.* Quite unlike the discrete, discernable events of parturition (ovulation, fertilization, the onset of contractions, delivery of the fetus and placenta, etc.), the mechanisms of parturition belong less to "phases" and more to the protean landscape of female reproductive physiology—so complex that medical science has yet to fully understand it. One example is progesterone withdrawal: in rats, it occurs

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rapidly, 2 days prior to the onset of labor, and triggers phase 2; in humans, progesterone withdrawal does not occur, and "phase 2" is a gradual progression from phase 1 to phase 3. Even so, out of respect for tradition and because we can repurpose it to our own teaching here, we retain and perpetuate the four *phases of parturition*. Again, we come at it from a very different perspective. At OME, **parturition** refers not to the birthing of young, but to the complex physiology of subduing the myometrium (phase 1: the progesterone-dominant state), preparing the myometrium for contraction (phase 2: the estrogen-dominant state), the contraction of the myometrium (phase 3: the oxytocin-dominant state), and the restoration of the myometrium to the prepregnant state (phase 4: the prolactin-dominant state). Four phases of "parturition." Each phase must consider the myometrium, endometrium, chorion, amnion, and fetus—the *layers of parturition.* And although the interaction between these layers essentially dictates the *phases of parturition*, we must also consider the impact of other maternal organs and endocrine axes, particularly oxytocin and prolactin. But first, the four phases.

Phase 1 of parturition is all about **myometrial quiescence**, making sure the uterus **doesn't contract**. The uterus must grow and stretch out with the fetus, but it must also be sustained in a manner that, when the time is right, it is able to expel baby. The myometrium must be kept silent but also ready to forcefully contract. Phase 1 (changing gears to the Dr. Williams version of the story) is **progesterone dominant** (more on this later in the lesson).

Phase 2 represents the changes in the myometrium, cervix, and decidual endometrium as they gradually prepare for phase 3. Phase 2 has traditionally been taught as being only a few weeks before phase 3, as if there were a rapid progression only nearing term. That's the rat physiology. Phase 2 begins when estrogen production overtakes progesterone production, and that happens around week 24. Phase 2 (again in Dr. Williams's version of this story) is **estrogen dominant**. It represents a gradual shift from the expression of genes that promote quiescence to the expression of genes that promote parturition. The closer to term a pregnancy is, the easier it is to induce labor, demonstrating that the initiation of labor results from an accumulation of changes and not from a sudden rush of events.

Phase 3 is **active labor**, the regular, forceful contraction of the myometrium that expels baby from the uterus, through the vagina, and into the world. Labor has three stages, which we discuss later in this lesson. Phase 3 is **oxytocin dominant**. We're fudging it a little by calling it "the oxytocin-dominant state," but we want to distinctly silo the phases, to show that phase 3 is very different from phase 2. In fact, labor involves many more signals than just oxytocin. But because once labor starts, it must finish, and because neither estrogen nor progesterone are in control, we use "oxytocin-dominant state" as a stand-in for local prostaglandins, neural reflexes from the cervix, and oxytocin from the posterior pituitary (more on this later). We just wanted to establish a mental image of phase 1 progesterone, phase 2 estrogen, phase 3 something else.

Phase 4 is the **recovery** of the uterus—myometrium and cervix—to the prepregnant state. But it also represents different physiology than that of simply being prepregnant. Phase 4 is the **prolactin-dominant state**. It is the withdrawal of progesterone and estrogen that unleashes the prolactin-driven breast milk axis, which takes over as the inhibitor of the HPO axis. It is also the absence of estrogen, progesterone, and baby that allows the uterus to return to the prepregnancy state. Therefore, the natural next step for mom is as the nutrient source for her young while development completes itself, after the fetus, now a neonate, is outside the womb.

Just as we will add a stage to the "stages of labor" (stage 4: don't forget that mom is still your patient), we add a phase to the phases of parturition. The prepregnant state is not typically considered in the phases of parturition, as the phases of parturition are traditionally taught in relation to the uterus. We at OME feel that if the phases of parturition include ovulation and fertilization, then there needs to be a phase that represents the time before that first phase. Thus, we have added to the traditional teaching of the

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phases, and we will refer to it as the resting, nonpregnant phase, **phase 0**. Traditionally, phase 4 is said to last 4–6 weeks because that is how long it takes for the uterus to return to normal. Remember that as long as mom breastfeeds, the oxytocin signal from suckling is used for the let-down reflex, and suckling sustains the prolactin-dominant state. Therefore, phase 4 lasts as long as mom continues to breastfeed.

	PHASE 0	PHASE 1	PHASE 2	PHASE 3	PHASE 4
Treating the myometrium as a puppy	N/A	Slumber time, no squeezy!	Hey, myometrium, hey, wake up!	SQUEEZE! SQUEEZE!	Job's done! Relax.
Traditional terminology	N/A	Myometrial Quiescence	Myometrial Awakening	Labor	Recovery
What's actually happening	Nonpregnant—ovarian and uterine cycles	Progesterone dominant	Estrogen dominant	Oxytocin dominant	Prolactin dominant

Table 6.1

Overview and Review of Crucial Physiology

CAPs. We again appropriate obstetrics concepts and define them more accurately; this time we focus on myometrial-contraction-associated proteins (CAPs). The myometrium can express oxytocin receptors, $PGF_{2\alpha}$ receptors, and connexins that form gap junctions. The more gap junctions, oxytocin receptors, and $PGF_{2\alpha}$ receptors the myometrium expresses, the more likely it is to go into labor. CAPs favor not just myometrial contraction (as their traditional definition implies) but also the onset of labor. The OME version of CAPs are not produced only by the myometrium but by any cell type. To the local environment of the uterus, it is particularly the expression of CAPs by the amnion, chorion, endometrium, and myometrium; all four layers talk to one another. As we will see in the next section, CAP transcription is **increased by estrogen** and decreased by progesterone. The intent of this paragraph is to establish that there are CAPs, not to dwell on the specifics of each CAP, which follow in this section.

QAPs. We at OME thought that if there were CAPs, there also ought to be **quiescence-associated proteins** (QAPs). Sure enough, there are, only no one named them that. So we did. CAP synthesis is just one way to regulate CAP production. The other is to regulate CAP degradation. For example, QAPs that degrade connexin, oxytocin receptors, and $PGF_{2\alpha}$ receptors favor quiescence. The only specific QAP we will teach you is BK_{Ca}, a **big potassium** (BK) channel that is activated by **calcium** (Ca). These are voltage-gated and calcium-gated (either stimulus opens these channels) potassium channels with **massive conductance** to potassium. The more of these channels there are in the plasma membrane of the myometrium, the more the myometrial smooth muscle cells will not depolarize and thus will not contract. QAP transcription is **increased by progesterone** and decreased by estrogen.

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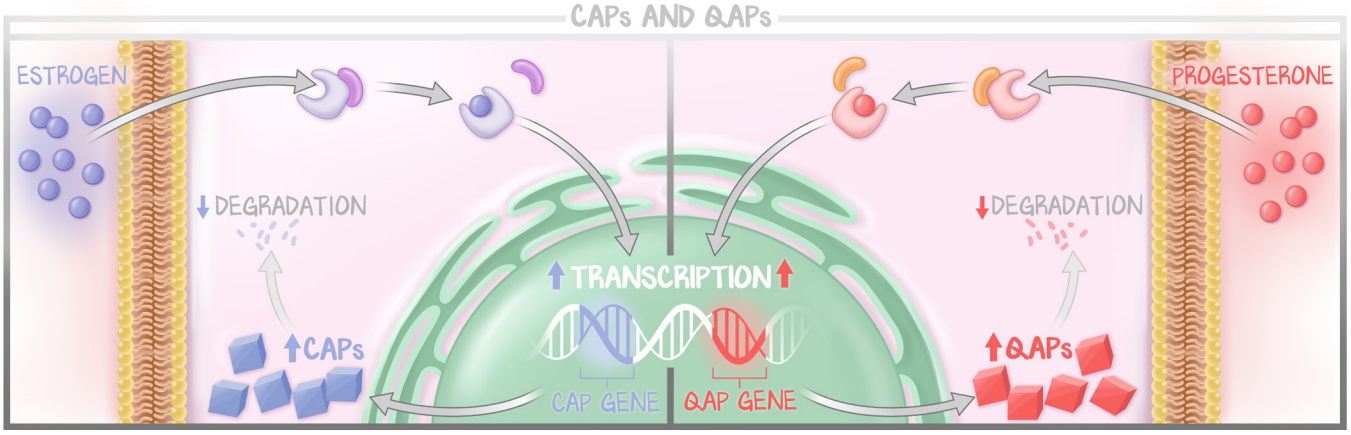

Figure 6.1: CAPs and QAPs
Estrogen favors myometrial contraction. Estrogen is a steroid hormone that regulates gene transcription. Estrogen upregulates the transcription of CAPs. Progesterone favors myometrial quiescence. Progesterone is a steroid hormone that regulates gene transcription. Progesterone upregulates the transcription of QAPs. There are, of course, more regulatory mechanisms (downregulation of gene transcription of the opposite, altering the expression of proteins that degrade CAPs or QAPs, etc.), but all you need to take away from this is progesterone, QAPs, quiescence; estrogen, CAPs, contraction.

You have engaged GPCRs, smooth muscle, and prostaglandins before. You have already seen what oxytocin does in the breast milk axis. These are not new concepts; to you, they are now innate knowledge. But in this lesson, they may appear like old friends wearing new fashions.

Smooth muscle and GPCRs. Smooth muscle is dilated—vasodilation, bronchodilation, and in this lesson, uterine quiescence—when there is cAMP or cGMP. This has been a fundamental, recurring theme throughout the curriculum, although we have previously focused on cGMP. In smooth muscle, the presence of either cAMP or cGMP means dilation. In the smooth muscle of the uterus, it means relaxation. The GPCR that uses **G_s** stimulates adenylyl cyclase and **induces more cAMP**. Nitrates, which become nitric oxide and stimulate adenylyl cyclase, and phosphodiesterase-5 inhibitors, which prevent the degradation of cAMP, have been used as tocolytics to prevent the delivery of a preterm infant. So have β_2 agonists, whose receptors use G_s. Therefore, we know that physiologically, GPCRs that act through G_s will keep the uterus quiescent. The immediate instinct is to think, *"if Gs relaxes, then Gi induces contraction."* You're not wrong, and that is sound logic. But in the myometrium, although G_s induces relaxation, G_i basically has no role. Instead, because the myometrium is smooth muscle, and therefore **calcium induces its contraction**, stimulation of the GPCR that acts through G_q (G_q-IP_3-Ca^{2+}) initiates contractions. Dihydropyridine calcium-channel blockers, such as nifedipine, have been used as tocolytics. **G_s stimulates quiescence through cAMP; G_i has no role; G_q stimulates myometrial contraction.**

Prostaglandins. In regard to the myometrium, there are three classes of prostaglandin receptors: the relaxation class (operating through G_s), the contractile class (operating through G_q), and the other one that isn't a major player in the myometrium (acting through G_i). The prostaglandins of parturition are PGE_2, $PGF_{2\alpha}$, and PGI_2. They are all synthesized from arachidonic acid by COX-2. The PG stands for prostaglandin. The 2 in the subscript is for the 2 in COX-2. Therefore, you can think of these prostaglandins as merely E, F, and I, greatly reducing their perceived complexity. Thankfully, at least for this subject, E and F (next to each other in the alphabet) both stimulate contractile-type GPCRs (G_q-IP_3-Ca^{2+}). E happens to be more potent than F. I stimulates relaxation-type GPCRs (G_s-cAMP relaxation). Said differently, the PGE_2 receptor and the $PGF_{2\alpha}$ receptor act through G_q-IP_3-Ca^{2+}, whereas the PGI_2 receptor acts through G_s-cAMP relaxation. In this sense, PGI_2 and the PGI_2 receptor are QAPs, whereas PGE_2, the PGE_2 receptor, $PGF_{2\alpha}$, and the $PGF_{2\alpha}$ receptor are CAPs.

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Oxytocin receptors. Both the decidualized endometrium and the myometrium express oxytocin receptors. Oxytocin receptors are also contractile-type GPCRs (G_q-IP_3-Ca^{2+}). For the myometrium, they are contractile-type GPCRs. In the decidualized endometrium, they act through G_q-IP_3-Ca^{2+} but don't cause contraction. Instead, they cause the expression of PGE_2 and $PGF_{2\alpha}$. Oxytocin receptors are also found on the posterior pituitary, from which oxytocin is secreted. All three tissue types are stimulated to express oxytocin receptors by estrogen. Oxytocin and oxytocin receptors are therefore CAPs.

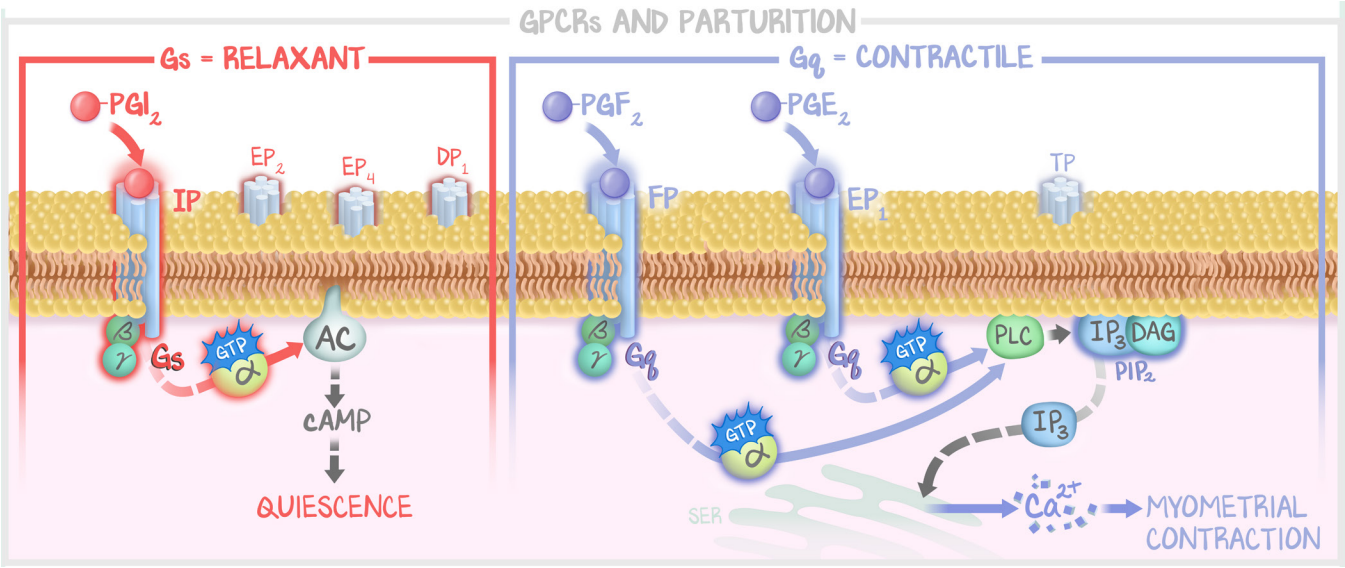

Figure 6.2: GPCRs and Parturition
There are many prostaglandin receptors. In the context of parturition, there are two receptor classes. Some induce myometrial quiescence, and some induce myometrial contraction. Like in any smooth muscle in the body, quiescence, the relaxation of smooth muscle, depends on the presence of cAMP (or cGMP). The GPCR that increases cAMP acts through G_s. PGI_2 receptors (I_2 receptors) act through G_s. Thus, PGI_2 (I_2) is a quiescent prostaglandin. The contraction of smooth muscle, like any smooth muscle in the body, is dependent on the presence of calcium in the cytoplasm. The GPCR that increases calcium is G_q. The PGF_2 receptor (F_2 receptor) and PGE_2 receptor (E_2 receptor) are GPCRs that use G_q; therefore, PGF_2 (F_2) and PGE_2 (E_2) are contractile prostaglandins.

Gene Transcription Regulation Drives Phases 1 and 2 and Causes Phase 3 to Begin

In rats, there is an abrupt withdrawal of progesterone that both heralds and induces the onset of delivery. In rats, the withdrawal of progesterone starts phase 2. But humans aren't rats, and a progesterone withdrawal doesn't happen in humans. What DOES happen is a relative switch from a progesterone-dominant state of gene transcription to an estrogen-dominant state of gene transcription due to a **relative shift in the progesterone-to-estrogen ratio**. So, humans are slightly more complex than rats—there is still a relative switch, it just isn't as large or as obvious as in rats.

The progesterone-dominant state transitions to the estrogen-dominant state at about the start of the third trimester, right around week 24. In the first two trimesters, **progesterone** promotes the transcription of genes that sustain the system (myometrium, endometrium, etc.) in a **quiescent phase**, stimulating the transcription of QAPs and inhibiting the transcription of CAPs. It both promotes QAPs and inhibits CAPs because exogenous administration of progesterone counteracts the administration of estrogen (in rat studies). Pregnancy is maintained, contractions do not occur, and CAPs have limited transcription and accelerated destruction. In the final trimester, in the **estrogen-dominant** state, estrogen overtakes progesterone as the primary driver of gene transcription. **Estrogen** promotes

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the transcription of genes that prepare the uterus for labor, stimulating the transcription of CAPs and inhibiting the transcription of QAPs. But what are they specifically, and where are they produced? Now we need to consider the amnion, chorion, endometrium, and myometrium separately.

In phase 1, the **quiescent phase**, the amnion makes prostaglandins, specifically PGE_2 and $PGF_{2\alpha}$. If the myometrium heard that signal, it would start contracting and initiate labor. The myometrium doesn't hear that signal because the chorion makes a molecule called prostaglandin dehydrogenase, effectively a **"prostaglandinase"** (degrades prostaglandins). There are far more than just prostaglandins in this process, including angiotensin 2, endothelin, oxytocin, and several other potential chemical signals. But only the prostaglandins have a clear role. In addition, the chorion has "oxytocinase," "enkephalinase," and "everythingelsenase." The point is that any signal the amnion can send to the myometrium is blocked by the chorion. In addition, the decidualized endometrium releases PGI_2, which stimulates I_2 receptors on the myometrium that lead to myometrial relaxation through G_s.

In phase 2, the **estrogen phase**, the myometrium, endometrium, and chorion undergo changes in genetic expression that convert the quiescent signaling to labor-inducing signaling. In the myometrium, estrogen induces the synthesis of connexins, $PGF_{2\alpha}$ receptors, and oxytocin receptors. In the endometrium, oxytocin receptors are synthesized along with $PGF_{2\alpha}$ and PGE_2, whereas the synthesis of PGI_2 is decreased. In the chorion, less "prostaglandinases" are produced. All the while, the amnion is making more and more prostaglandins. In the anterior pituitary, estrogen had already been driving the proliferation of lactotropes, and now in the estrogen phase, stimulates the synthesis and release of oxytocin. It is a feedforward effect, driven by estrogen, that makes the myometrium and endometrium express oxytocin receptors while inducing the posterior pituitary to make more oxytocin. The end result is sufficient inhibition of QAP gene transcription and sufficient stimulation of CAP gene transcription that finally pushes the myometrium past the threshold, and contractions begin.

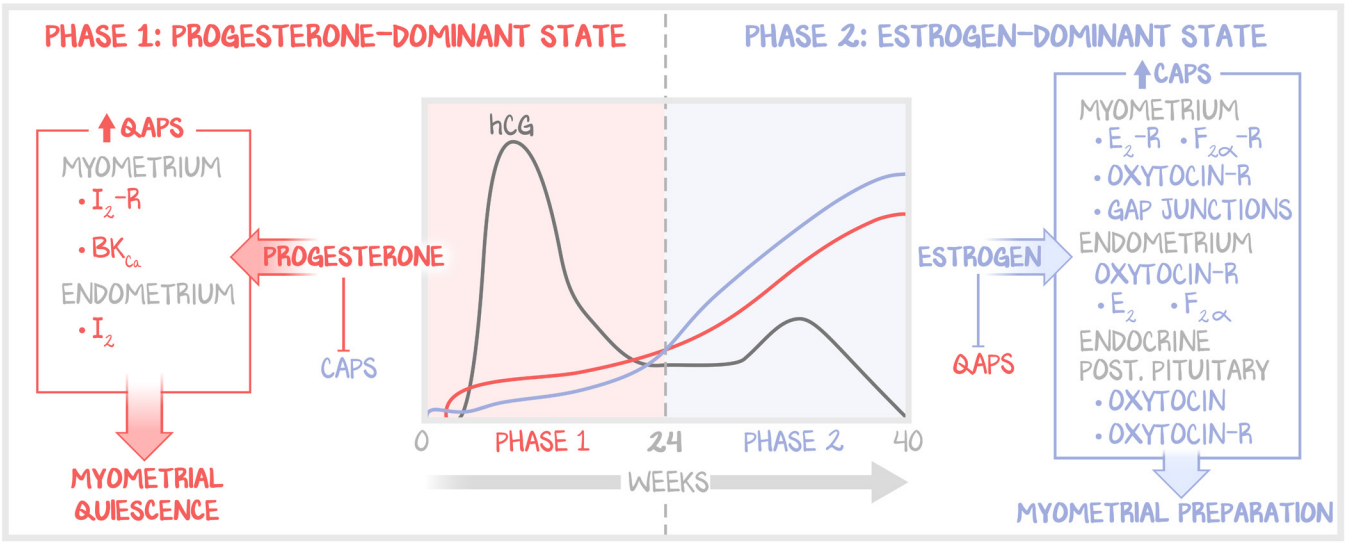

Figure 6.3: Relative Progesterone Withdrawal
In rats, an abrupt withdrawal of progesterone initiates myometrial contraction and the onset of delivery. Humans work similarly; we're just more complicated. Phase 1, the first and second trimesters, is dominated by progesterone and the expression of QAPs. Progesterone and estrogen steadily increase throughout pregnancy. Phase 2 starts at the beginning of the third trimester, as estrogen levels overtake progesterone levels. Now in an estrogen-dominant state, gene regulation favors CAPs. Any time progesterone is withdrawn (pharmacologically), evacuation of the uterus via myometrial contractions will start. Without progesterone withdrawal (as is normal in humans), the initiation of the evacuation of the uterus via myometrial contractions (here, termed labor) is caused by an oxytocin surge (not illustrated).

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In phase 3, the **oxytocin phase**, the **phase of labor**, the *phase of parturition* that is also the *stages of labor*, myometrial contractions begin. Because the myometrium is smooth muscle, what mom perceives as painful contractions that come and go are actually the pain associated with myometrial fibers shortening; yet between mom's contractions, the smooth muscle of the myometrium does not relax. Latching enables the uterus to maintain increased tone. Once initiated, contractions become more regular and more intense. Phase 3 of parturition has three stages of labor, discussed separately in this lesson. Oxytocin does not participate in phase 2. Oxytocin and oxytocin receptors are upregulated during phase 2, shifting the myometrium and endometrium from a progesterone-dominant state through the estrogen-dominant state, and into an oxytocin-dependent state.

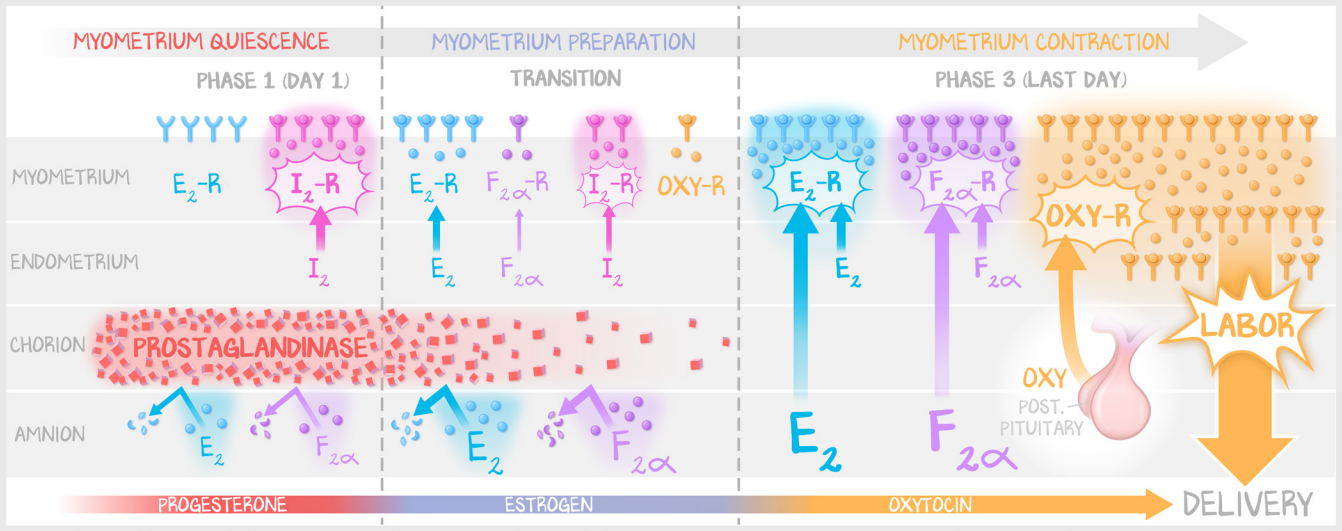

Figure 6.4: Snapshots of Phase 1 and Phase 2
In the beginning, in phase 1 of parturition, the amnion (embryo and amniotic sac) is small and therefore does not produce many contractile prostaglandins; the chorion expresses a lot of prostaglandinase, the endometrium emits quiescent prostaglandins, and the myometrium expresses both E_2 receptors (contractile receptors) and I_2 receptors (quiescence receptors). Only the quiescent message is delivered and heard. At the end, the beginning of phase 3, the receptor and enzyme expression have reversed. The chorion expresses little to no prostaglandinase; the amnion is large (ready for delivery) and emits massive amounts of E_2 and $F_{2\alpha}$ (contractile prostaglandins). The endometrium has stopped expressing I_2 and now emits E_2 and $F_{2\alpha}$. The myometrium has upregulated its expression of E_2 receptors and $F_{2\alpha}$ receptors while downregulating I_2 receptors. In addition, oxytocin receptors are now expressed by the endometrium and myometrium. The maternal oxytocin surge will initiate labor. Like the HPO axis and ovulation, where alterations in gene expression prepare the system for the LH surge and ovulation, so too has estrogen prepared this system for the "oxytocin surge" and delivery. Phase 2 of parturition changes the system from the progesterone-dominant quiescence of phase 1 to the oxytocin-dominant contractions of phase 3. The changes from phase 1 to phase 3 are directed by an estrogen-dominant state during phase 2.

This is an oversimplification, as pregnancies, including delivery, can proceed in animals with anterior pituitary resections. Stretching of the uterus by a growing fetus likely also alters gene transcription, ever favoring labor as the fetus grows. Further implications are found in the cortisol system, an interplay between the fetus's cortisol and ACTH levels (though it appears that the cortisol axis is more like a timer than the cause of the initiation of labor). Much like cortisol levels spiking just before waking, so too does baby's cortisol spike prior to delivery. We understand we are breezing over this paragraph, hand-waving away some complexity because everything in this paragraph is probably true but hasn't been confirmed. So, we stick with what is known to be the case and what fits with human biology.

In phase 4, mom is breastfeeding. We covered the regulation of breastfeeding in the Breast island.

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We Know This Due to Empirical Data—Induction of Labor

Without any doubt, progesterone withdrawal results in parturition. In humans, that progesterone withdrawal can be pharmacologically induced. **Selective progesterone receptor modulators** (SPRMs) with antagonistic properties in the myometrium (most infamously **mifepristone**, also known as U-486) are effective at initiating labor at **every phase of parturition**, at any gestational age. Induction of labor before viability is a medically terminated pregnancy. Induction of labor at term is just delivery. In addition, labor occurs hours to days after administration, after the relative amounts of estrogen dominate over the massively decreased effective amount of progesterone.

PGE_2 receptors are expressed in myometrial cells all the time. We know this because PGE_1 (**misoprostol**) and PGE_2 analogs (**dinoprostone**) are applied to the cervix topically to induce labor. These, too, can be used at any gestational age. When administered to the cervix or vagina, cervical ripening (discussed below) and muscular contractions begin. These are less effective in later term as monotherapies, and oxytocin infusion is often added, indicating the changes throughout gestation that prepare the myometrium for multiple signals.

$PGF_{2\alpha}$ receptors are expressed in small quantities in phase 1 but expressed in increasing numbers close to term. **Carboprost** is a $PGF_{2\alpha}$ analog. It can be used to induce labor, especially later in pregnancy. But it is more often used in the treatment of **postpartum hemorrhage**, especially in patients who fail other therapies. This would only cause the uterus to contract down more, to squeeze off open blood vessels. Thus, it stimulates uterine contraction, but most effectively at the end of gestation.

The infusion of oxytocin is used both to initiate labor and to improve the power of the uterus, to make it contract harder. It is not possible to use oxytocin to induce labor in the first trimester, indicative of the lack of oxytocin receptors on the myometrium. In the second trimester, it is possible but requires huge doses. The **closer to term** gestation is, **the lower the oxytocin dose required**. This informs us that there is an ever-increasing number of oxytocin receptors and amount of oxytocin being produced over time.

We Know This Due to Empirical Data—Prevention of Labor

We don't discuss preterm labor or its management in the Basic Sciences. And, to be frank, almost every study on pharmacological intervention for the prevention of labor—**tocolysis**—either resulted in unfavorable outcomes (β_2 agonists killing mom) or found that the intervention was only safe for up to 48 hours. Two days is a long time for a preterm fetus. ACOG does recommend their use (but only up to 48 hours), and there is usually no appreciable benefit. BUT! This is the Basic Sciences, where we focus on mechanisms. Despite the failure of pharmacological intervention to provide meaningful (statistically significant) benefits, the study of tocolytics reinforces what we know to be true about the quiescent phase.

Because smooth muscle relies on calcium influx in order to contract, **dihydropyridine calcium-channel blockers** (specifically **nifedipine**) have been used to delay preterm labor. The nondihydropyridine calcium-channel blockers (diltiazem and verapamil) do not have tocolytic effects.

The β_2 noradrenergic receptor acts through G_s. Just as β_2 activation induces skeletal muscle dilation and bronchodilation, **β_2 agonists** can induce myometrial relaxation. **Terbutaline** is the drug of choice for this effect. It has limited efficacy and can only delay delivery for hours to minutes. **Ritodrine** was pulled from the market because it caused **an increase in acute respiratory distress syndrome**. Yet, it is how medical science determined that G_s, acting through the dilatory properties of cAMP, is one mechanism for subduing the myometrium, especially early in the progesterone-dominant state.

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Coming off the efficacy of β_2 agonists, and having identified cAMP as the quiescent signal, **phosphodiesterase-5 inhibitors** (specifically **sildenafil**) have been used to delay the onset of labor. The decreased decomposition of cAMP to AMP sustains more cAMP, and thus more relaxation. Used in combination, oral nifedipine and transvaginal sildenafil can delay the onset of labor for up to 7 days. **Nitrates**, which would increase the amount of cAMP (although we want you to learn it as cGMP in vascular smooth muscle cells), are also effective at delaying labor. The precipitous drop in blood pressure that accompanied the use of nitroglycerine directed researchers away from it.

COX-2 inhibitors (NSAIDs, in particular) prevent the generation of prostaglandins. NSAIDs were once thought to be a huge windfall for preterm labor. Specifically, indomethacin was used. Like the drugs above, there could be a mild delay in the labor onset. "*End*omethacin ends" the patent ductus, and so administering NSAIDs to a pregnant woman will result in the process of ductus arteriosus closure, so delivery must follow quickly after its administration. The impairment of clotting also makes NSAIDs unsuitable. But again, their use demonstrated how important prostaglandins are in the initiation and maintenance of labor.

The Cervix Throughout Phases 1 and 2

The cervix consists of its endometrium—simple columnar epithelium that invaginates to form glands—and stroma. The cervix produces a protective barrier (preventing organisms from entering the uterine cavity while pregnant), must maintain competency (stay closed) for the duration of almost all of pregnancy, then must dilate to let baby out in less than 24 hours, then go back to normal over the course of a week. The **endometrium** secretes a thick mucus called the **mucous plug**. When cervical dilation begins, the mucous plug is released, resulting in a "bloody show." The cervical **stroma** does not have a multitude of cells like that of the uterine cavity. We are not dragging you into a discussion regarding proteoglycans, collagen fibrils, and glycosaminoglycan-associated proteins of the ground substance of the extracellular space of the uterus. **Cervical stroma** is **the extracellular matrix** (and the fibroblasts that maintain it), and thus the proteins within the stroma determine the cervix's shape and function. If stuff is held together, the cervix is firm. If stuff isn't held together, the cervix is soft. Stuff is held together by **disulfide bonds**. The fewer the disulfide bonds, the less well held together and the softer the cervix. **Hyaluronic acid** is a special extracellular molecule that is an enormously long string of carbohydrates without the ability to form bonds. Hyaluronic acid holds onto water. The more hyaluronic acid, the softer the cervix.

During **phase 1** of parturition, the cervix undergoes what is termed **cervical softening**. "Softening" means **hyperplasia** of the epithelia and the **remodeling of collagen**. Collagen is constantly remodeled wherever it is present. The extracellular matrix is made of collagen, interlinking molecules, and bonds. The fewer there are of those interlinking bonds, the looser the extracellular matrix becomes. Cervical softening is the hyperplasia of the epithelium so the epithelium can be dilated. Softening is also the beginning of the extracellular remodeling to make the stroma more amenable to stretching.

During **phase 2** of parturition, the cervix undergoes what is termed **cervical ripening**. Cervical ripening is not a physiological term. It was used to mean whether or not "a successful vaginal delivery was most likely" using a **Bishop score**. That is correct: phase 2 of parturition is merely the continued remodeling of the extracellular matrix that enables dilation and effacement. There continues to be remodeling of the extracellular proteins, with fewer disulfide bonds formed. During cervical ripening, **excess hyaluronic acid is made**. Hyaluronic acid does not form bonds with other hyaluronic acid molecules. It holds onto water in great abundance. It is what makes cartilage such an excellent shock absorber, capable of being deformed but returning to its shape while not breaking. It is what gives the cervix its consistency at the beginning of pregnancy ("like the tip of your nose"). In excess, there is even more water, and the cervix becomes even more capable of being deformed, giving it the consistency just before delivery ("like your lip"). The hyperplasia during phase 1 enables the epithelium to be stretched out. The hyaluronic acid of phase 2 enables the stroma (extracellular matrix) to be stretched out.

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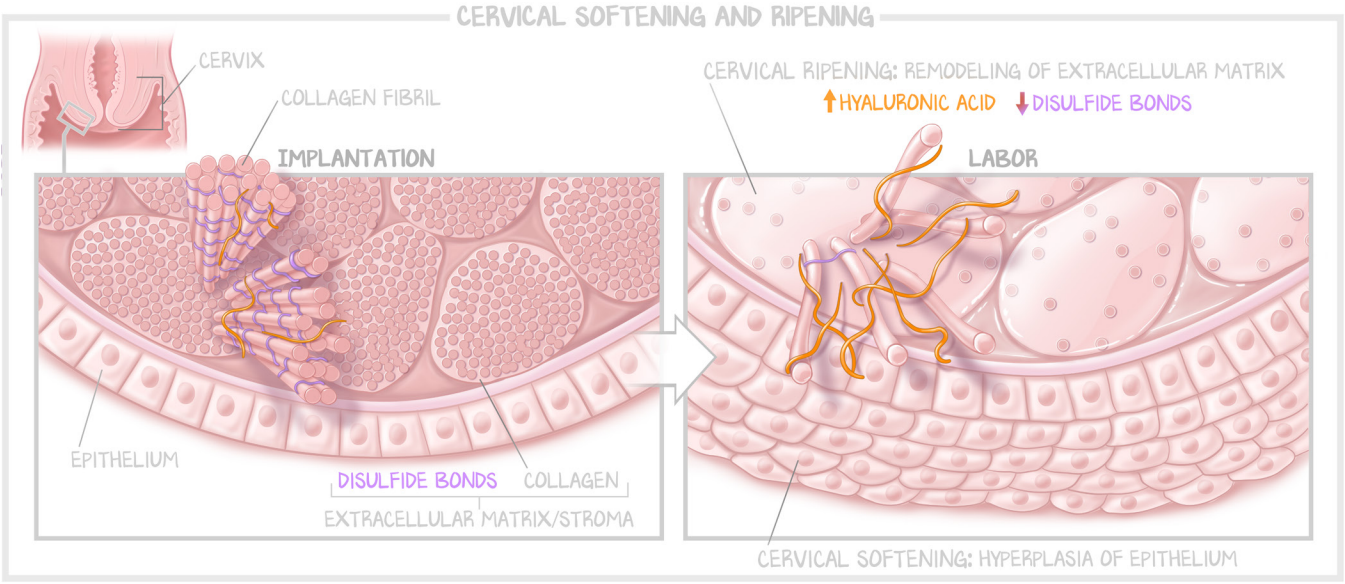

Figure 6.5: Cervical Softening and Ripening
In preparation for effacement and dilation at the time of delivery, the cervix undergoes cervical softening and ripening. Cervical softening is a product of epithelial hyperplasia (depicted here as a stratified epithelium, although in truth, there is just extra simple columnar epithelium, and this depiction is was chosen as the mechanism to represent extra cells). Cervical softening is the remodeling of the extracellular matrix to become very loose connective tissue. This is achieved by synthesizing extracellular matrix proteins with fewer disulfide bonds and more hyaluronic acid. Hyaluronic acid enables the extracellular matrix to hold more water. Fewer disulfide bonds enable the proteins of the extracellular matrix to move, to become pliable. Both more water and more pliability mean the cervix can change its shape quickly and with little resistance.

Phase 3: Labor and the Three Stages of Labor

Phase 3 of parturition is labor. Labor has three stages: effacement and dilation, delivery of the fetus, and delivery of the placenta. There are norms of how fast each stage should progress, cutoffs and values we are not going to report to you. We will in Clinical Sciences. Here, we want to stay focused on the anatomical and physiological changes.

Stage 1: Effacement and Dilation. The myometrium is composed of a **lower uterine segment**, which is confluent with the cervix and **does not contract**, and an **upper uterine segment,** which contracts and **does not relax**. Rather, the upper uterine segment **shortens its sarcomeres** with active contractions (the pain mom feels), but because it is smooth muscle, it need not lengthen while not actively shortening. When there is an active shortening of the myometrium, mom will experience pain, perceived by mom as a contraction. But after shortening, the myometrium will not lengthen. This engages the fetus's head against the cervix and exerts continuous downward pressure on the cervix. This results in stronger myometrial contraction through the **Ferguson reflex**. As labor progresses, what mom perceives as contractions (active shortening of the myometrial muscle fibers) become more frequent and more coordinated. Baby cannot be birthed until mom's cervix has reached **maximal dilation** (approximately 10 cm). The upper uterine segment decreases in size through the shortening of the muscle fibers. Baby can't change volume; it can only be birthed. And since the birthing process cannot happen until maximal cervical dilation, there must be some sort of volume change somewhere. As discussed above, the cervix was undergoing the processes of **softening** in stage 1 of parturition and **ripening** in phase 2. Now it is both dilating (the opening getting wider) and undergoing **effacement**. The ripened cervix dilates by becoming shorter, contributing its overall volume to its diameter rather than its height. Effacement is the shortening of the cervix to a miniscule height (so short that it can no longer be appreciated with the naked eye, where effacement gets its name). The cervix is pulled up and around baby's head. Thus there

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is very little movement of baby, but rather changes in the uterus that enable it to constantly contract against baby, contracting the upper uterine segment and opening the cervix to enable baby's passage through the vagina (known as the birth canal). The cervix dilates from a diameter of 0 cm to 10 cm.

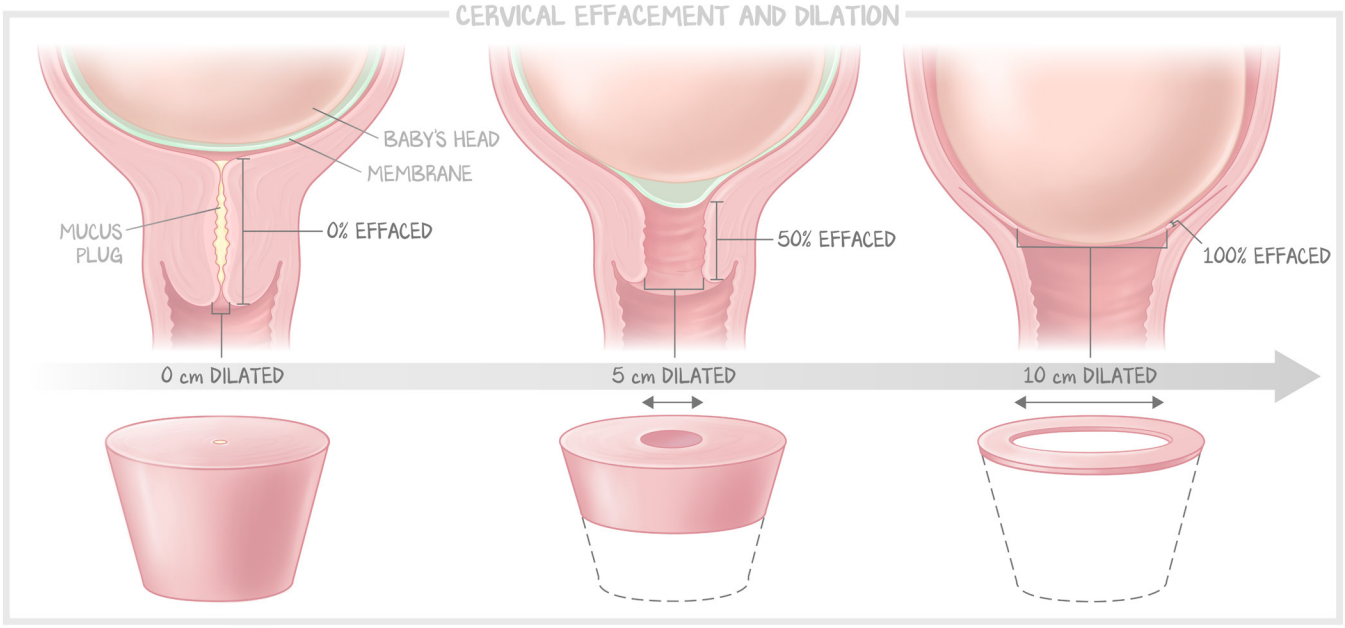

Figure 6.6: Cervical Effacement and Dilation
The cervix will become both shallower (effacement) and wider (dilation). The tissue volume required to dilate comes from the shortening of the cervix and the "softening" proliferation of the epithelium. The ability to make such drastic changes quickly comes from the cervical "ripening," making the stroma extracellular matrix loose connective tissue and mostly water.

Stage 2: Delivery of the fetus. The way the myometrium reacts to baby at the cervix is to get shorter at the cervix and lower uterine segment, thereby decreasing the overall height of the uterus. This has a beneficial conformational shape that orients baby's head and spine more vertically—aiming them at the birth canal. Contractions of the myometrium thus expel baby by pushing down. From 10-cm dilation to fetal expulsion is stage 2. Complications, abnormal labor, and the "cardinal movements of labor" are reserved for Clinical Sciences.

Stage 3: Delivery of the placenta. With the rapid expulsion of baby, the myometrium continues to contract downward, both decreasing in size and exerting the same forces on the placenta as it did on the fetus. The chorion is attached to the endometrium of the stratum functionale, sometimes referred to as the decidua spongiosa. The stratum basale does not require the stratum functionale. As the uterus decreases in size, it causes the amnion-chorion-decidua combination to buckle, forming folds as it does. This separates the chorionic villi from the maternal circulation and a hematoma forms between them. The hematoma grows, effectively dissecting the connection between the placenta-decidua and the myometrium; the placenta separates from the stratum basale, taking with it the chorionic villi, the amnion, and the decidua spongiosa (the stratum functionale), and they are expelled from the uterus.

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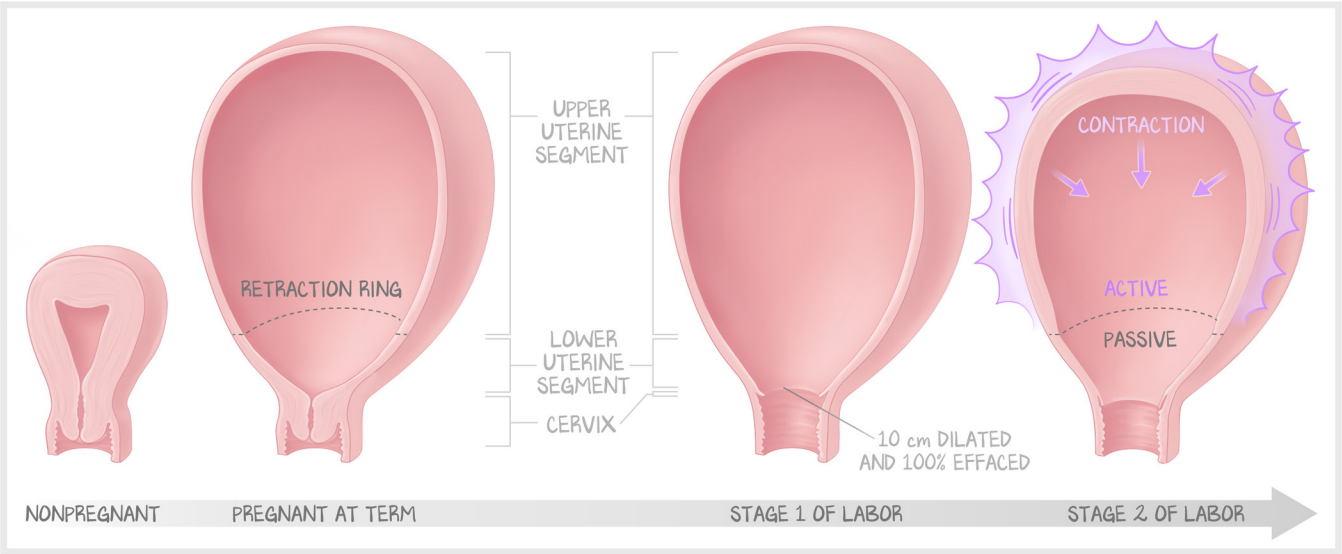

Figure 6.7: Upper and Lower Uterine Segments
As contractions begin, the upper uterine segment contracts downward. This pushes baby's head against the cervix, the signal for the cervix to undergo effacement and dilation. The myometrium will not loosen up—it is smooth muscle. If the upper uterine segment is getting smaller but baby isn't moving, something has to give. That something is the lower uterine segment up to the retraction ring. By the time the cervix is fully effaced and dilated, the crown of baby's head has already passed the boundary of the cervix and is already in the vaginal lumen.

Stage 4: Mom. This is not a traditional stage of labor, but one that we include to remind the learner that just because the placenta is out of mom doesn't mean your care of mom is done. There are complications following delivery that are not part of phase 4 of parturition or stage 3 of labor. Mom just birthed a child, so attend to her status and her needs, and let the pediatrician deal with the neonate.

Phase 4: Puerperium

The puerperium is the period of 4–6 weeks after childbirth, during which mom's pelvic reproductive organs return to the prepregnant state. Once again, nomenclature fails us—puerperus means childbearing, the state of the mother prior to parturition (parturient), yet the puerperium is the time after parturition. Don't get hung up on the term; see it as phase 4, when the uterus goes back to normal. Everything has to go back to the prepregnant state, or at least close to it. It took 9 months to build the uterus to the state it was in, then less than a day to completely alter the cervix and expel all of its contents. The contraction of the smooth muscle cells facilitates the expulsion of the fetus and placenta, but then radical changes take place over the ensuing 4–6 weeks that restore a relatively normal prepregnant uterus.

In the **myometrium**, **atrophy** (not hypoplasia, necrosis, or apoptosis) of the smooth muscle cells of the myometrium is the most remarkable change. A uterus at term is near 1,000 g but is only 500 g 1 week after birth, and 100 g (normal uterine mass) by week 3. The deconstruction of contractile fibers accounts for this change. Actin and myosin are degraded, and the volume of the uterus shrinks. The **number of myocytes does not change**.

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In the **endometrium**, proliferative changes restore the endometrium to its prepregnant state. At the site of placental insertion, however, there is often no stratum basale present, only a bleeding wound. There is an increased number of immune cells in the decidualized endometrium at the time of delivery. Those "immune cells" were not there to defend against infection or facilitate the expulsion of the fetus and its placenta. The "immune cells" are neutrophils, macrophages, and fibroblasts, present to do what they do everywhere—**wound healing**. Thus, at the **site of placental insertion**, neutrophils gobble up baddies and die in place while calling for help, while macrophages clear the field, and fibroblasts transform the clotted blood into a scar. At the same time, the stratum basale of the endometrium on the flanks of the placental insertion site proliferate. This proliferation **re-epithelializes** the endometrium, new proliferation pushing off the old, decidualized, and now necrotic endometrium of pregnancy. The stratum basale at the margins of the site of the placenta proliferate to replace the lost stratum basale. There are both fibroblasts forming scar and the stratum basale forming new endometrium. Not all of the placental insertion site is repaired, so some areas of a multigravida uterus will be scar and not endometrium. This is why multiple pregnancies increase the risks of placenta previa and placenta accreta.

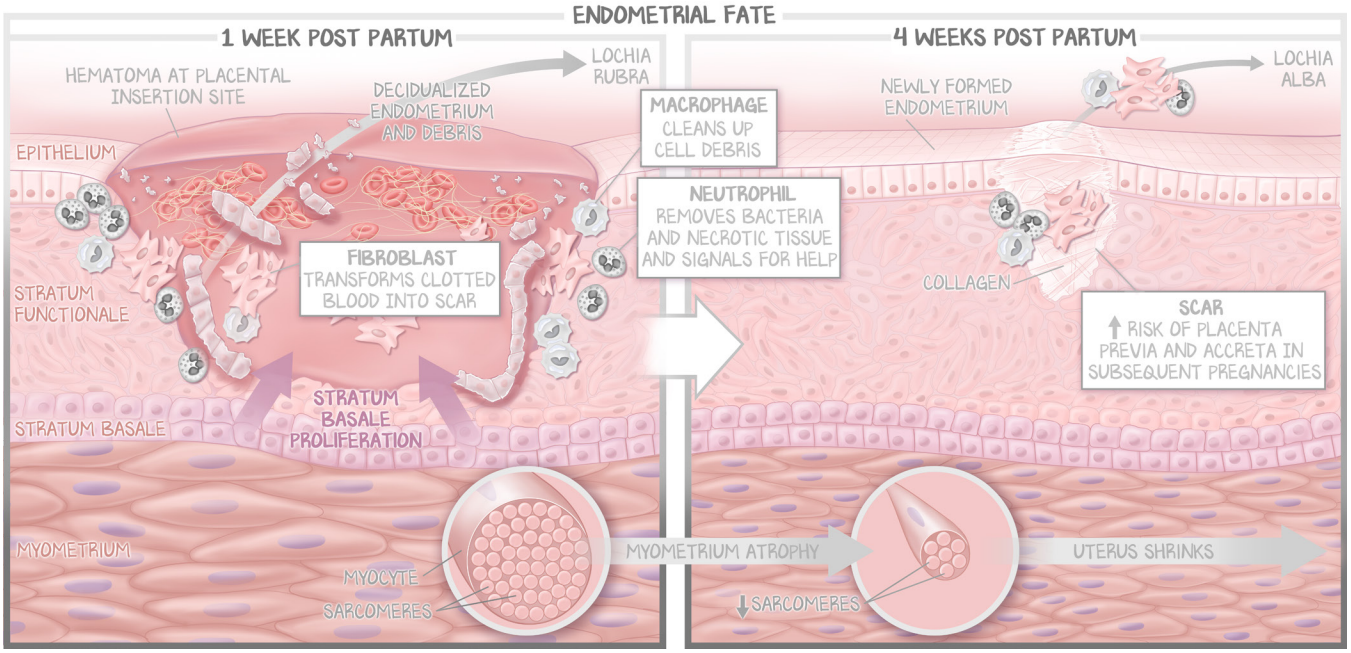

Figure 6.8: Endometrial Fate
The placentation site fills with a hematoma as the placenta is ejected. There is a rapid shrinkage of the uterine myometrium. The number of cells do not change, but rather the sarcomere content changes. The endometrium will be repaired by neutrophils, macrophages, fibroblasts (scar), and proliferation of the stratum basale. The scar will make for poor placentation in the future.

Over the ensuing 4–6 weeks following delivery, the contents of the gravid uterus are expelled, but slowly. **Lochia** is the normal vaginal expulsion of the decidua and cellular debris of the pregnancy and may easily be confused with postpartum hemorrhage. Lochia is effectively the result of the uterus cleaning itself out. In the beginning, there are many red blood cells that formed the hematoma and the fibrin clots that sealed the bleeding shut. Thus the lochia that comes out after the first week is red, called lochia rubra. It transitions through a serous fluid appearance, called lochia serosa. Finally, as the fibroblasts use the clots as scaffolding, the redness disappears and is replaced by lochia rich in the immune cells, fibroblasts, and scar. Lochia alba is white. The most important thing to understand about lochia is that there will be **immune cells present for the duration that lochia is expressed**. It is the expected presence of immune cells, cells of inflammation, in the uterus that renders postpartum

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evaluation of endometrial tissue for infection futile. If there is a postpartum fever, the presence of immune cells in the endometrial tissue cannot be used to make the diagnosis of an infection. Obstetric complications are discussed in Clinical Sciences.

The **cervix** gradually returns to its original size and shape, the undoing of effacement and dilation, over 2 days. It doesn't go all the way back to its original size and shape, however. It will effectively protect and gestate a future baby, but it is now more capable of effacing and dilating. The more deliveries a woman has had, the easier and faster a healthy delivery will go.

The changes to the **abdominal wall**, **uterine ligaments**, and **stretched skin** of the abdomen take 6 weeks to return to normal. Exercise accelerates this healing. Exercise should begin as soon as mom can stand up after delivery – ambulation in the postpartum setting is the single best way to avoid DVTs. The perinatal period remains a hypercoagulable state, and mobility significantly decreases the risk of forming DVTs.

LARC is recommended by ACOG following any pregnancy. Although breastfeeding should suppress ovulation, LARC is simple to place and replace and will ensure that mom will not get pregnant again. The idea is that mom endured significant stress throughout pregnancy and delivery, and will have all of her resources dedicated to her newborn, so best not to make her endure pregnancy again while still caring for an infant.

We discussed the postpartum diuresis and the return to normal GFR in the lesson on the physiology of pregnancy and lactation in the Breast island.

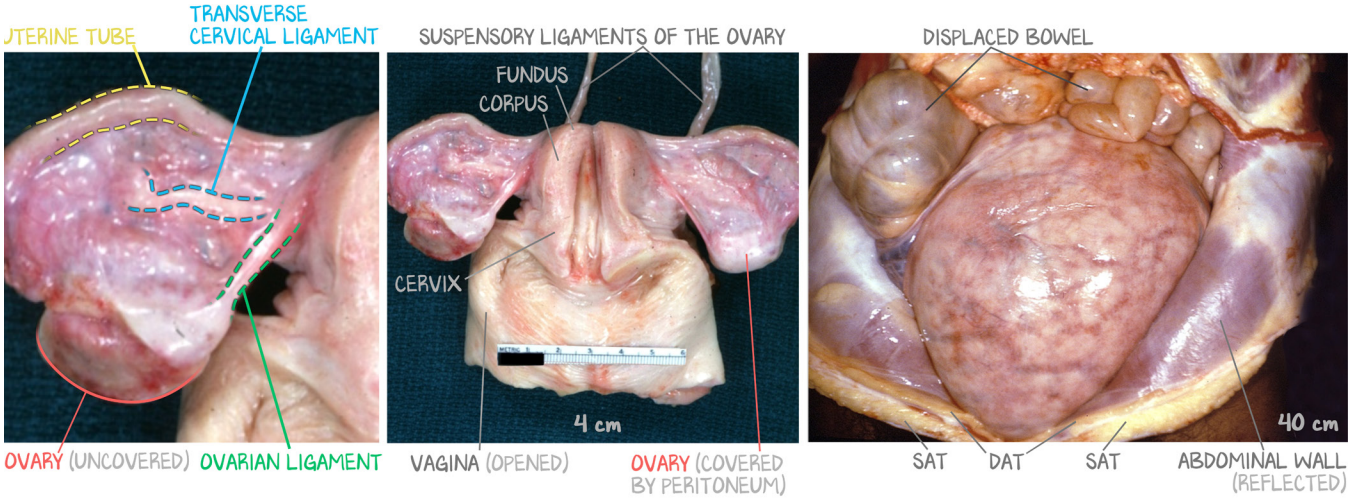

Figure 6.9: Comparing a Nulligravid Uterus to a Fully Gravid Uterus
A nongravid uterus is close to 4 cm in length. In this image, the uterus and vagina have been sectioned and butterflied open. A gravid uterus is 40 cm in length. This autopsy shows how displaced the abdominal contents can become at full term. The superior adipose tissue (SAT), deep adipose tissue (DAT), and internal musculature of the abdomen are labeled for orientation. In the zoomed image, the relative anatomy of the uterine tubes, ovaries, and connecting ligaments can be seen in relation to the broad ligament, which drapes over the uterine tube at the top, and then drapes both forward and back, over the adnexa, with all the contents remaining below, and not within, the peritoneal cavity. Not depicted is the peritoneal cavity, which would be above the uterine tube and fundus of the uterus, which are lined with the peritoneal cavity's lining, commonly referred to as the broad ligament.

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